

## WHAT'S NEW IN THE PSYCHOPHARMACOLOGY OF SCHIZOPHRENIA \*

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THE most exciting statement about what is new in the drug treatment of schizophrenia would be that we can improve the likelihood of remission or amelioration of the illness. Unfortunately, we cannot say that. We have hit a ceiling on the therapeutic efficacy of drugs. There is no convincing evidence that any of the antipsychotics introduced since chlorpromazine are more effective, and, aside from promazine, once considered a useful antipsychotic, there is no firm evidence that any of more than two dozen marketed drugs or those in the investigational pipeline have any more or less therapeutic activity. This is remarkable because antipsychotics are no longer variations of the phenothiazine molecule, but come from diverse chemical classes that appear to have little in common. The best present explanation is that all active antipsychotics block dopamine receptors. Further support for this hypothesis comes from the close correlation between ability to block dopamine and antipsychotic potency. This leaves unexplained why we have reached a ceiling.

New developments concern refinements of drug treatment, new drugs under development, and new knowledge concerning adverse reactions.

### MAINTENANCE TREATMENT

The value of antipsychotic drugs in relieving the psychotic symptoms of schizophrenia is undeniable, but indications for long-term treatment are less well established. John Davis<sup>1</sup> showed that in the 24 controlled studies

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comparing an antipsychotic to a placebo in which treatment lasted for at least a month, superiority of the active drug is impressive. These data are less helpful than they appear at first because the clinician is interested in answers to specific questions concerning his patients and not global results covering a very heterogeneous group. The clinician wants to know whether long-term treatment is needed after three months, six months, one year, etc. Does it make a difference if the patient is still very ill? Does it matter if the patient has had one episode or many? Recent work has supplied some answers.

In recent years the indication for long-term antipsychotic drugs in outpatient schizophrenics has been subject to several controlled studies. Pasamanick et al.<sup>2</sup> showed that most schizophrenics referred to a state hospital could be better treated as outpatients if given trifluoperazine. This important study is not relevant to the prevention of relapse or deterioration because patients entered during their acute or exacerbating phase. Whether schizophrenics who reached a full or partial remission should be maintained on drugs remains unanswered.

Engelhardt et al.<sup>3</sup> compared chlorpromazine and promazine to placebo treatment in outpatient schizophrenics. The chlorpromazine group did best, but the study lacked clear diagnostic criteria and had a high drop-out rate, nor was a distinction made between those in remission and those not. Possibly drugs might effectively prevent worsening of a psychotic schizophrenic yet be ineffective in preventing a return of psychosis in a patient in remission.

The next important study was done by Leff and Wing in Great Britain,<sup>4</sup> who selected 35 outpatient schizophrenics, all carefully diagnosed and in full remission of psychosis. For one year chlorpromazine or trifluoperazine were compared to placebo. Eighty-three percent of the placebo group relapsed, as opposed to 33% of the drug patients, a statistically significant difference. This study is difficult to interpret from the small size of the sample and its narrow selection because patients that psychiatrists considered too ill for placebo or too well for active drug therapy were excluded from the study. This confuses the issue of general prognosis and prediction of drug responsiveness. That we can predict with some success who has a better prognosis does not mean that the course can or cannot be improved by maintenance medication.

Hogarty et al.<sup>5</sup> studied recently discharged schizophrenics randomly assigned to sociotherapy, i.e., individual casework and vocational rehabili-

tation, or to minimal contact and to drug treatment—chlorpromazine or placebo. Each patient was studied for two years. They did not divide patients according to degree of remission, but the result of drug treatment is clear-cut. After two years 80% of the placebo patients had relapsed, against 48% of those on chlorpromazine. Counseling had no significant effect.

With Drs. Quitkin and Klein, I studied aftercare schizophrenics<sup>6,7</sup> in full remission treated by oral fluphenazine, fluphenazine decanoate, or placebo for one year. The results were advantageous to the active treatment. Approximately 10% of those receiving both types of fluphenazine relapsed as compared to 64% of the placebo group, a highly statistically significant difference.

The placebo-controlled long-term outpatient study by Hirsch et al.<sup>8</sup> compared fluphenazine decanoate to placebo, and after nine months 66% of placebo patients and 8% treated by fluphenazine had relapsed.

The conclusion from placebo-controlled studies represents a distinct advance in knowledge: outpatient schizophrenics, in remission or not, should receive antipsychotic medication for one to two years. A possible exception might be the group with the best prognosis, i.e., those with a good premorbid history who had one episode with full recovery. There is no evidence about maintenance treatment in this group, one way or another. It seems reasonable that if any subgroup of schizophrenics might not need maintenance drugs, it would be these because the possibility of recurrence without drug treatment may be very low. We are currently collecting data on this question.

#### NEW ANTIPSYCHOTICS

The most important recent addition to our armamentarium has been long-acting depot fluphenazine enanthate and decanoate. Drug treatment of outpatients is often severely hampered by covert noncompliance,<sup>9,10,11,12</sup> and long-acting depot compounds seem to be an important way to deal with this problem. However, the advantage of fluphenazine decanoate or enanthate over active oral drugs for outpatient schizophrenics has not been clearly demonstrated. Double-blind comparisons between oral antipsychotics and one of the injectable fluphenazines by Crawford and Forrest,<sup>13</sup> our group,<sup>6,7</sup> Hogarty et al.,<sup>14</sup> and Schooler et al.<sup>15</sup> found no statistically significant differences in relapse rates. Only the study by Del Giudice et al.<sup>16</sup> did so. Fluphenazine enanthate was superior to oral fluphenazine.

It is puzzling why the injectable drug is not clearly superior given the known high incidence of covert noncompliance in pill taking. Probably, patients selected for participation in double-blind studies are especially compliant, and closely supervising them throughout the study may enhance compliance. We consider depot drugs best for any outpatient in whose compliance the clinician lacks complete confidence. There is also the theoretical possibility that the incidence of tardive dyskinesia may be less with depot drugs because the total dose is much smaller than with oral treatment, although the total dose to the brain may be the same because the initial passage through the hepatic portal system is omitted.

### HIGH DOSAGE

Increasing dosage has been tried to gain more efficacy from present drugs. Following the lead of French reports, four double-blind controlled studies compared very high doses of fluphenazine to standard doses. High dose is an understatement here—megadose is more appropriate, megadoses ranging from 800 to 1200 mg./day. In equivalent chlorpromazine units that would be 40,000 to 60,000 mg./day. Three studies dealt with chronic schizophrenics hospitalized for long periods and resistant to standard treatments. All three found the megadosage superior to standard high doses of 30 to 60 mg./day,<sup>17,18,19</sup> but in the published reports did not indicate that improvement was sufficient to allow discharge.

We and Donald Klein studied hospitalized nonchronic schizophrenics who had not responded to at least six weeks of standard drug treatment,<sup>20</sup> but who had not been in hospital more than two months. The two dosages were 1,200 and 30 mg./day. We found no advantage to the megadosage, and, in fact, the lower dose group did better. The improvement rate on the standard dose was unexpectedly high—60%, i.e., the additional six weeks of standard dose was sufficient to bring most of this group into remission.

The other three megadose studies used very chronic patients who were refractory to treatment. Thus, schizophrenics should not be considered refractory to standard doses after only six weeks of treatment. The value of megadosage to long-term chronic patients remains problematic. Even if such massive doses do produce some improvement, is it worth the increased risk of tardive dyskinesia if the clinical improvement is not substantial enough to permit return to the community?

A remarkable finding in all megadose studies is that such enormous doses of fluphenazine are relatively well tolerated. The original French

observations are confirmed in that matter; once past a threshold the increase in extra pyramidal side effects typically seen as the dose of fluphenazine approaches 30 mg./day, reaches a plateau or diminishes. This phenomenon is unexplained.

### HIGH DOSE IN ACUTE PATIENTS

Several recent studies reported the use of substantial doses of parenteral antipsychotic medication rapidly to control agitated psychotic patients: doses of haloperidol up to 30 mg. and chlorpromazine 50 mg. every 30 to 60 minutes.<sup>21-26</sup> Two controlled studies of such regimens<sup>27-28</sup> convincingly demonstrated the usefulness of frequent parenteral high doses to ameliorate severe symptoms. It has not been demonstrated whether such rapid calming is relevant to the rapidity or quality of the eventual maximal response to treatment.

### NEW ANTIPSYCHOTIC DRUGS

What new drugs are appearing? There are several new depot antipsychotics such as perphenazine enanthate, flupenthixol decanoate, pipotiazine undecylate, and fluspirilene. None is on the market here nor has it been demonstrated that these drugs are more effective or less toxic than available fluphenazine esters.

A unique new drug is penfluridol, a long-acting oral agent given at only weekly intervals. Its effectiveness and toxicity seem comparable to other drugs,<sup>29-33</sup> but a once-weekly oral drug would be a decidedly worthy addition to our armamentarium.

Unfortunately, penfluridol has recently been associated with animal toxicity. In rats treated for 24 months a statistically significant increase in pancreatic tumors and a statistically nonsignificant increase in mammary tumors were found compared to placebo-treated animals. The Federal Drug Administration withdrew the drug from further human testing until the risk to humans has been more fully assessed.

Molindone is a new antipsychotic from a chemical class (hydroindolones) not structurally related to other antipsychotics. Its effectiveness as an antischizophrenic drug is well documented,<sup>34-37</sup> and its toxicity is similar to high-potency phenothiazine. It does have a unique characteristic: it is associated with weight loss<sup>34,36,38</sup> and, because many drug-treated schizophrenics are overweight, this makes molindone an attractive drug.

Loxapine is another recent antipsychotic, a member of another new

class. Its efficacy and toxicity are similar to other antipsychotics.<sup>39-44</sup> Post hoc analysis of the data from controlled studies suggests that loxapine may be particularly useful in paranoid schizophrenia,<sup>45</sup> and prospective studies are currently underway to test this possibility.

The most fascinating new drug to appear in recent years is clozapine. Like loxapine, it is a benzoxazepine, but, unlike all other known antipsychotics, it does not seem to cause extrapyramidal side effects.<sup>46-48</sup> That a drug can be antipsychotic without causing extrapyramidal side effects is of marked theoretical and practical importance. Of practical importance is the hope that a drug which does not cause reversible neurological adverse reactions will not cause tardive dyskinesia. There is preliminary evidence that clozapine can reverse tardive dyskinesia.<sup>48</sup> Unfortunately, a high incidence of agranulocytosis associated with this drug was recently found in Finland.<sup>49</sup> At present, in this country clozapine is available for investigational purposes only.

#### TARDIVE DYSKINESIA

The most important recent news in the drug treatment of schizophrenia has been our growing awareness of tardive dyskinesia. The prevalence varies enormously: according to published accounts it is 0 to 40%.<sup>50</sup> The wide differences are probably due to different samples and differing definitions of the toxicity. Few facts are known about it. It is related to the use of antipsychotic medication, and is more common among elderly people. Whether related to the total cumulative dose, duration of treatment, or both is not known, nor whether any particular drug is more culpable. Data relevant to these issues are extremely difficult to obtain because they require not only an accurate numerator, drug use in instances of the syndrome, but an accurate denominator, the same information in similar patients who do not develop it. Such ratios for different drugs at differing dosages, while accounting for such possibly relevant factors as age, sex, diagnosis, dental condition, and impairment of the central nervous system, will be very difficult to obtain, and it is now unlikely ever to be done.

No treatment of tardive dyskinesia has been established, and proposed treatments have not withstood scrutiny. The list of candidates includes dopamine-depleting drugs such as reserpine or tetrabenazine,<sup>51</sup> dopamine itself,<sup>52</sup> cholinergic drugs<sup>53-55</sup> including deanol,<sup>56-62</sup> L-tryptophan,<sup>63</sup> lithium,<sup>64</sup> methylphenidate,<sup>65</sup> isocarboxate,<sup>66</sup> and even dopamine agonists.<sup>67</sup>

The most consistent finding is that antipsychotic drugs can relieve the syndrome, but this is usually a short-term success and long-term loss leading to a vicious cycle. As mentioned earlier, clozapine may be effective, and, not being a strong dopamine blocker, may not cause re-emergence of the condition.<sup>68</sup>

The best treatment of tardive dyskinesia is to stop the antipsychotic drug. If done early enough, remission is common.<sup>69</sup> If removal of the antipsychotic leads to exacerbation of the schizophrenia this poses a dilemma to be resolved on the basis of the severity of the symptoms and the impact of the toxicity or the illness upon the patient's life.

In the absence of an established treatment, prevention must be stressed. Antipsychotics should be used for long-term treatment only when necessary and when it is the drug of choice—which means at present—for schizophrenia. Valid short-term use, as for agitated depression or mania, poses little risk.

### CONCLUSION

We conclude this survey of new developments in the drug treatment of schizophrenia with the observation that we are being squeezed in two directions. It is now clearer that long-term treatment can ameliorate the morbidity of schizophrenia, and yet simultaneously we are increasingly sensitive to the serious danger of long-term treatment. Our hopes must be pinned on better drugs that are more effective and safer. There have been some steps in that direction, but the drug treatment of schizophrenia leaves much room for improvement.

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